

WEST Search History

DATE: Monday, February 04, 2008

<u>Hide?</u>	<u>Set Name</u>	<u>Query</u>	<u>Hit Count</u>
		<i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR</i>	
<input type="checkbox"/>	L40	L37 and FK506	14
<input type="checkbox"/>	L39	L37 and rapamycin	11
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<input type="checkbox"/>	L19	L16 and (5000)adj(daltons)	8
<input type="checkbox"/>	L18	L15 and intracellular	0
<input type="checkbox"/>	L17	L14 and targeting	50
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<input type="checkbox"/>	L8	L4 and (5)adj(kD)	9
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<input type="checkbox"/>	L5	L2 and targeting	0
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NEWS	31	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS	32	JAN 28	MARPAT searching enhanced
NEWS	33	JAN 28	USGENE now provides USPTO sequence data within 3 days of publication
NEWS	34	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment
NEWS	35	JAN 28	MEDLINE and LMEDLINE reloaded with enhancements

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2,

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	ENTRY	SESSION
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=> s conjugate
L1 294316 CONJUGATE

=> s l1 and rapamycin
L2 171 L1 AND RAPAMYCIN

=> s l2 and cyclosporin
L3 58 L2 AND CYCLOSPORIN

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L4 17 L3 AND FK506

=> dup remove l4
PROCESSING COMPLETED FOR L4
L5 14 DUP REMOVE L4 (3 DUPLICATES REMOVED)

=> s l5 and pd<19991119
2 FILES SEARCHED...
L6 4 L5 AND PD<19991119

=> d l6 1-4 cbib abs

L6 ANSWER 1 OF 4 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights
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1997097360 EMBASE Prevention and treatment of acute graft-versus-host disease: The old and the new. A report from the Eastern Cooperative Oncology Group (ECOG). Lazarus H.M.; Vogelsang G.B.; Rowe J.M.. Dr. H.M. Lazarus, Department of Medicine, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106, United States. Bone Marrow Transplantation Vol. 19, No. 6, pp. 577-600 2 Mar 1997.

Refs: 374.

ISSN: 0268-3369. CODEN: BMTRE9

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 970422. Last Updated on STN: 970422

AB There have been many advances in the prevention and treatment of GVHD, including cyclosporine, FK506, and combination therapies. This syndrome, however, continues to account for significant morbidity and mortality after allogeneic transplantation. With the expanded use of matched unrelated as well as mismatched related donors, the increase in incidence and severity of GVHD poses a new clinical challenge. Many of the newer agents discussed in this paper may have a role in the future as therapy for acute GVHD. The evaluation of these new agents and the approach to be taken is hampered by the realization that most patients have received and are relatively refractory to standard therapies. Clinical trials must be performed earlier in the course of the syndrome to establish the role of these compounds. Newer strategies are likely to include the use of sequential therapy directed at blocking endogenous cytokines followed by blocking alloreactive donor cells, and immunologic advances such as the induction of tolerance. What impact, if any, such therapy may have on amelioration of a graft-versus-leukemia effect remains unknown.

L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

1999:390464 Document No. 131:39762 Method to identify transcriptional modulators. Verdine, Gregory L.; Nyanguile, Origene (President and Fellows of Harvard College, USA). PCT Int. Appl. WO 9930164 A1 19990617, 90 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US26101 19981209. PRIORITY: US 1997-987912 19971209.

AB Novel synthetic transcriptional modulators having at least one selected ligand linked to at least one transcriptional modulating portion are described. The transcriptional modulators of the present invention can include a ligand linked to a chemical moiety. These transcriptional modulators can be used to selectively control gene expression and to identify components of the transcriptional machinery.

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

1998:398286 Document No. 129:64041 Self-enhancing, pharmacologically controllable gene expression systems. Muller, Rolf; Sedlacek, Hans-Harald (Hoechst A.-G., Germany; Aventis Pharma Deutschland GmbH). Eur. Pat. Appl. EP 848061 A2 19980617, 56 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1997-121752 19971210. PRIORITY: DE 1996-19651443 19961211.

AB The invention relates to a nucleic acid construct which constitutes a self-enhancing expression system and which comprises the following components: at least one first structural gene that encodes an active compound; at least one second structural gene that encodes a transcription factor protein; and at least one activation sequence comprised of at least one sequence that binds the transcription factor protein and at least one promoter sequence. Each activation sequence activates the expression of a structural gene and the expression of the transcription factor protein. The nucleic acid construct can be used for preparing a drug for treating diseases.

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

1995:881452 Document No. 123:296614 Pretargeting methods and compounds with

reduced immunogenicity of targeting moiety-anti-ligand **conjugates** or other components employed in diagnostic and therapeutic pretargeting protocols. Graves, Scott S.; Bjorn, Michael J.; Reno, John M.; Axworthy, Donald B.; Fritzberg, Alan R.; Theodore, Louis J. (Neorx Corp., USA). PCT Int. Appl. WO 9515770 A1 **19950615**, 173 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US14223 19941209. PRIORITY: US 1993-164302 19931209.

AB Methods, compds., compns., and kits that relate to pretargeted delivery of diagnostic and therapeutic agents are disclosed. In particular, methods and agents are provided for reducing the immunogenicity of targeting moiety-anti-ligand **conjugates** or other components employed in diagnostic and therapeutic pretargeting protocols. Preparation of various **conjugates** for use in the invention is included. Examples include e.g. in vivo anal. of a radiolabeled chelate-biotin **conjugate** administered after antibody pretargeting, clearing agent evaluation, two- and three-step pretargeting methodol., administration of a monoclonal antibody (MAb)-streptavidin **conjugate** in humans, and immunosuppression of MAb-containing **conjugates**.

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L7 3 LL2 AND DIMER

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4 FILES SEARCHED...

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L10 0 L2 AND (LESS THAN 5000 DALTON)

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PROCESSING COMPLETED FOR L11

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=> d l12 1-13 cbib abs

L12 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

1999:390464 Document No. 131:39762 Method to identify transcriptional modulators. Verdine, Gregory L.; Nyanguile, Origene (President and Fellows of Harvard College, USA). PCT Int. Appl. WO 9930164 A1 **19990617**, 90 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US26101 19981209. PRIORITY: US 1997-987912 19971209.

AB Novel synthetic transcriptional modulators having at least one selected ligand linked to at least one transcriptional modulating portion are described. The transcriptional modulators of the present invention can include a ligand linked to a chemical moiety. These transcriptional modulators can be used to selectively control gene expression and to identify components of the transcriptional machinery.

L12 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

1998:398286 Document No. 129:64041 Self-enhancing, pharmacologically controllable gene expression systems. Muller, Rolf; Sedlacek, Hans-Harald (Hoechst A.-G., Germany; Aventis Pharma Deutschland GmbH). Eur. Pat.

Appl. EP 848061 A2 19980617, 56 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1997-121752 19971210. PRIORITY: DE 1996-19651443 19961211.

AB The invention relates to a nucleic acid construct which constitutes a self-enhancing expression system and which comprises the following components: at least one first structural gene that encodes an active compound; at least one second structural gene that encodes a transcription factor protein; and at least one activation sequence comprised of at least one sequence that binds the transcription factor protein and at least one promoter sequence. Each activation sequence activates the expression of a structural gene and the expression of the transcription factor protein. The nucleic acid construct can be used for preparing a drug for treating diseases.

L12 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

1998:760149 Document No. 130:29213 Glycoconjugates of antitumor drugs with improved in vivo compatibility. Bosslet, Klaus; Czech, Joerg; Gerken, Manfred; Straub, Rainer; Blumrich, Matthias (Hoechst A.-G., Germany). Ger. Offen. DE 19720312 A1 19981119, 8 pp. (German). CODEN: GWXXBX. APPLICATION: DE 1997-19720312 19970515.

AB A composition containing a **conjugate** Glycosyl-Y[C(:Y)X]pW(R)nXC(:Y)A (Glycosyl = enzymically cleavable poly-, oligo-, or monosaccharide; W = aromatic or heteroarom. residue, aliphatic residue with conjugated double bounds, or amino acid residue which cyclizes after cleavage of the glycosyl residue; R = H, Me, OMe, CO₂H, CN, CO₂Me, OH, NO₂, F, Cl, Br, SO₃H, SO₂NH₂, alkylsulfonamide; X = O, NH, CH₂O, CH₂NH, CH₂NMe, etc.; Y = O, NH; A = antitumor agent; p = 0, 1; n = integer), a sugar and/or sugar alc., a divalent ion, and a pharmacol. acceptable carrier shows enhanced antitumor activity with decreased side effects compared to the unconjugated drug. Preferably the **conjugate** is more hydrophilic than the unconjugated drug, and the spacer group is spontaneously cleaved by chemical hydrolysis. Thus, i.v. administration of a composition containing N-[4-O-(β-D-glucopyranosyluronic acid)-3-nitrobenzyloxycarbonyl]doxorubicin Na salt (I) (400 mg/kg) in 0.9% NaCl solution containing 5% mannitol and CaCl₂ to LoVo tumor-bearing mice on days 1, 4, and 8 considerably slowed tumor growth and decreased mortality compared to controls receiving I alone or combined only with mannitol.

L12 ANSWER 4 OF 13 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1998138091 EMBASE Immunological treatment of autoimmune diseases. Kalden J.R.; Breedveld F.C.; Burkhardt H.; Burmester G.R.. J.R. Kalden, Department of Internal Medicine III, Institute for Clinical Immunology, University Hospital, Erlangen-Nurnberg, Germany. Advances in Immunology Vol. 68, pp. 333-418 1998.

Refs: 27.

ISSN: 0065-2776. CODEN: ADIMAV

Pub. Country: United States. Language: English.

Entered STN: 19980514. Last Updated on STN: 19980514

L12 ANSWER 5 OF 13 MEDLINE on STN

DUPLICATE 1

1998105687. PubMed ID: 9444942. The MDR1 (P-glycoprotein) and MRP (P-190) transporters do not play a major role in the intrinsic multiple drug resistance of Jurkat T lymphocytes. Martel J; Payet M D; Dupuis G. (Department of Biochemistry, Faculty of Medicine, University of Sherbrooke, Quebec, Canada.) Leukemia research, (1997 Nov-Dec) Vol. 21, No. 11-12, pp. 1077-86. Journal code: 7706787. ISSN: 0145-2126. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The response of T cells in relation to the cell cycle has not been extensively studied. We have attempted to address this question using Jurkat T cells treated with cytostatic drugs known to arrest cells at various transition points of their cycle. We tested several concentrations of drugs that act at G1/S (hydroxyurea, lovastatin, thymidine), early S (aphidicolin, cyclosporin A,

rapamycin) or G2+M (colchicine, nocodazole) in 24 h cultures. Cytofluorimetric analyses showed that cycling Jurkat cells were equally distributed between the G1 (44.9 +/- 6.5%) and S (42.3 +/- 8.0%) phases. Cell distribution in G2+M was 12.7 +/- 2.8%. Hydroxyurea but not lovastatin increased the percentage of cells in S phase to approximately 60-70% and both drugs decreased it to approximately 30% in G1. Thymidine had no effects. Aphidicolin increased the distribution in S phase to approximately 70% with a decrease in G1 to approximately 30%. **Cyclosporin A** and **rapamycin** increased the percentage of the cells in G1 to approximately 70% and decreased it to approximately 25% in S phase. Nocodazole increased cell distribution in G2+M to approximately 60% and induced a decrease in G1 to approximately 10%. The effects of the drugs were not related to their toxicity and their limited efficiency raised the possibility that Jurkat cells possessed an intrinsic resistance to these xenobiotics. Time-course analysis showed (scanning electron microscopy) that the early morphological changes induced by colchicine were reversible. Drug efflux experiments (vinblastine) suggested that an ATP-dependent process could be involved. However, Northern blot analyses showed a weak signal for MDR1 (P-glycoprotein). In contrast, a probe for MRP (P-190) showed a strong signal in Jurkat and peripheral lymphocytes. The presence of drugs (**cyclosporin A**, nocodazole, thymidine) (24 h) did not upregulate its message and cell treatment with DL-butathione (S,R)-sulfoximine only moderately affected the efficiency of the glutathione S-conjugate MRP transporter. Our data suggest that the intrinsic multidrug resistance of leukemic Jurkat T cells does not appear to involve the MDR1 and MRP members of the ABC family of reverse drug transporters and these observations raise the possibility of the involvement of multifaceted mechanisms.

L12 ANSWER 6 OF 13 MEDLINE on STN DUPLICATE 2
 1998026431. PubMed ID: 9379682. The MDR1 (P-glycoprotein) and MRP (P-190) transporters do not play a major role in the intrinsic multiple drug resistance of Jurkat T lymphocytes. Martel J; Payet M D; Dupuis G. (Department of Biochemistry, Faculty of Medicine, University of Sherbrooke, Quebec, Canada.) Leukemia research, (1997 Aug) Vol. 21, No. 8, pp. 743-52. Journal code: 7706787. ISSN: 0145-2126. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The response of T cells in relation to the cell cycle has not been extensively studied. We have attempted to address this question using Jurkat T cells treated with cytostatic drugs known to arrest cells at various transition points of their cycle. We tested various concentrations of drugs that act at G1/S (hydroxyurea, lovastatin, thymidine), early S [aphidicolin, **cyclosporin A** (CsA), **rapamycin**] or G2 + M (colchicine, nocodazole) in 24 h cultures. Cytofluorimetric analyses showed that cycling Jurkat cells were equally distributed between the G1 (44.9 +/- 6.5%) and S (42.3 +/- 8.0%) phases. Cell distribution in G2 + M was 12.7 +/- 2.8%. Hydroxyurea but not lovastatin increased the percentage of cells in S phase to ca 60-70% and both drugs decreased it to ca 30% in G1. Thymidine had no effects. Aphidicolin increased the distribution in S phase to ca 70% with a decrease in G1 to ca 30%. CsA and **rapamycin** increased the percentage of the cells in G1 to ca 70% and decreased it to ca 25% in S phase. Nocodazole increased cell distribution in G2 + M to ca 60% and induced a decrease in G1 to ca 10%. The effects of the drugs were not related to their toxicity and their limited efficiency raised the possibility that Jurkat cells possessed an intrinsic resistance to these xenobiotics. Time-course analysis showed (scanning electron microscopy) that the early morphological changes induced by colchicine were reversible. Drug efflux experiments (vinblastine) suggested that an ATP-dependent process could be involved. However, Northern blot analyses showed a weak signal for MDR1 (MDR, multiple drug resistance). In contrast, a probe for multidrug resistance-associated protein (P-190; MRP) showed a strong signal in Jurkat and peripheral lymphocytes. The presence of drugs (CsA, nocodazole, thymidine) (24 h) did not up-regulate its message and cell treatment with BSO only moderately affected the

efficiency of the glutathione S-**conjugate** MRP transporter. Our data suggest that the intrinsic multidrug resistance of leukemic Jurkat T cells does not appear to involve the MDR1 and MRP members of the ABC family of reverse drug transporters and these observations raise the possibility of the involvement of multi-faceted mechanisms.

L12 ANSWER 7 OF 13 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1997097360 EMBASE Prevention and treatment of acute graft-versus-host disease: The old and the new. A report from the Eastern Cooperative Oncology Group (ECOG). Lazarus H.M.; Vogelsang G.B.; Rowe J.M.. Dr. H.M. Lazarus, Department of Medicine, University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106, United States. Bone Marrow Transplantation Vol. 19, No. 6, pp. 577-600 2 Mar 1997.

Refs: 374.

ISSN: 0268-3369. CODEN: BMTRE9

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 970422. Last Updated on STN: 970422

AB There have been many advances in the prevention and treatment of GVHD, including cyclosporine, FK506, and combination therapies. This syndrome, however, continues to account for significant morbidity and mortality after allogeneic transplantation. With the expanded use of matched unrelated as well as mismatched related donors, the increase in incidence and severity of GVHD poses a new clinical challenge. Many of the newer agents discussed in this paper may have a role in the future as therapy for acute GVHD. The evaluation of these new agents and the approach to be taken is hampered by the realization that most patients have received and are relatively refractory to standard therapies. Clinical trials must be performed earlier in the course of the syndrome to establish the role of these compounds. Newer strategies are likely to include the use of sequential therapy directed at blocking endogenous cytokines followed by blocking alloreactive donor cells, and immunologic advances such as the induction of tolerance. What impact, if any, such therapy may have on amelioration of a graft-versus-leukemia effect remains unknown.

L12 ANSWER 8 OF 13 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1996311883 EMBASE Antirejection strategy in small bowel transplantation. Wood R.F.M.. R.F.M. Wood, Clinical Sciences Centre, Northern General Hospital, Sheffield S5 7AU, United Kingdom. Transplantation Proceedings Vol. 28, No. 5, pp. 2491-2493 1996.

ISSN: 0041-1345. CODEN: TRPPA8

Pub. Country: United States. Language: English.

Entered STN: 961112. Last Updated on STN: 961112

L12 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

1995:881452 Document No. 123:296614 Pretargeting methods and compounds with reduced immunogenicity of targeting moiety-anti-ligand **conjugates** or other components employed in diagnostic and therapeutic pretargeting protocols. Graves, Scott S.; Bjorn, Michael J.; Reno, John M.; Axworthy, Donald B.; Fritzberg, Alan R.; Theodore, Louis J. (Neorx Corp., USA). PCT Int. Appl. WO 9515770 A1 19950615, 173 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US14223 19941209. PRIORITY: US 1993-164302 19931209.

AB Methods, compds., compns., and kits that relate to pretargeted delivery of diagnostic and therapeutic agents are disclosed. In particular, methods and agents are provided for reducing the immunogenicity of targeting moiety-anti-ligand **conjugates** or other components employed in diagnostic and therapeutic pretargeting protocols. Preparation of various **conjugates** for use in the invention is included. Examples include e.g. in vivo anal. of a radiolabeled chelate-biotin **conjugate** administered after antibody pretargeting, clearing agent evaluation, two- and three-step pretargeting methodol., administration of a monoclonal

antibody (MAb)-streptavidin **conjugate** in humans, and immunosuppression of MAb-containing **conjugates**.

L12 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

1995:294145 Document No. 122:185334 Homogeneous immunoassays using **conjugates** of analytes and substituted analogs of glucose-6-phosphate dehydrogenases. Jakobovits, Edward B.; Silen, Joy L.; Levy, Mark J.; Goodman, Thomas C.; Becker, Martin J.; Ullman, Edwin F.; Caldwell, Robert M.; Bott, Richard R.; Barnett, Christopher Charles (Syntex (U.S.A.) Inc., USA; Genencor International Inc.). PCT Int. Appl. WO 9424559 A2 **19941027**, 121 pp. DESIGNATED STATES: W: CA, FI, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US3437 19940407. PRIORITY: US 1993-44857 19930408.

AB Immunoassays using mutant forms of glucose-6-phosphate dehydrogenase (G6PDH) as labels are described. In particular, the assays use **conjugates** of an analyte or analyte analog and a mutant NAD⁺-dependent G6PDH. Typically, the mutations involve deletion or substitution of lysine residues or introduction of cysteine residues. The preparation of such analogs of Leuconostoc G6PDH by site-directed mutagenesis and expression of the cloned genes and the conjugation of analytes to the enzyme analogs are described. Assays for antibodies to analytes that measured the inhibition of G6PDH conjugated with the analytes by the antibodies are described.

L12 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

1994:212008 Document No. 120:212008 Methods and reagents for the determination of immunosuppressive agents and their binding proteins. Lane, Benjamin Clay; Luly, Jay Richard; Smith, Allan H.; Bolling, Timothy J.; Mandecki, Wlodozimir; Pilot-Matias, Tami J. (Abbott Laboratories, USA). PCT Int. Appl. WO 9325533 A1 **19931223**, 53 pp. DESIGNATED STATES: W: AU, CA, JP, KR; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US5197 19930601. PRIORITY: US 1992-893858 19920605.

AB Assay methods and reagents for determining the presence or amount of immunophilin ligands and immunophilins thereof employing a recombinant fusion protein comprising (i) an immunosuppressant binding protein and (ii) a heterologous protein are disclosed. The recombinant fusion protein can also be employed for the evaluation of immunosuppressive activities of immunosuppressive agents in order to determine their efficacy during the course of therapeutic treatment of a patient. Preferably, the recombinant fusion protein comprises a macrolide immunosuppressive agent and CTP: CMP-3-deoxy-D-manno-octulosonate cytidyl transferase (CKS). When employed in a binding assay format, the recombinant fusion protein provides higher reactivity for the immunophilin ligand under determination than does the native immunosuppressant binding protein. Also provided are ascomycin (or FK-506) and **rapamycin** analog **conjugates** with macromols. or detectable moieties. In particular, an immunosuppressant assay reagent comprising recombinantly-prepared human FK-506 binding protein (FKBP)-CKS fusion protein immobilized on a solid support material provides a higher signal-to-noise ratio when employed in a competitive heterogeneous assay format than when native FKBP immobilized on a solid support material is employed in such assay format. Ascomycin-C22-carboxymethyloxime-alkaline phosphatase **conjugate** was also prepared and used as a reagent in assays.

L12 ANSWER 12 OF 13 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1993077508 EMBASE Transplant rejection: Mechanisms and treatment. Chandler C.; Passaro Jr. E.. Dr. E. Passaro Jr., Surgical Service, Veterans Affairs Medical Center, Los Angeles, CA 90073, United States. Archives of Surgery Vol. 128, No. 3, pp. 279-283 **1993**. ISSN: 0004-0010. CODEN: ARSUAX
Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 930418. Last Updated on STN: 930418

AB In this review, we summarize the cellular and molecular events in the rejection of transplanted allografts, as well as the rationale for the evolving techniques to suppress such rejection. Allogenic major histocompatibility complex antigens expressed on the allograft and/or on the 'passenger leukocytes' within the graft are the major antigenic stimuli recognized as being foreign by receptors of CD4+/T helper cells of the host. Host macrophages provide a second signal, interleukin (IL) 1, essential to the activation of T helper cells. Subsequent production of IL-2 by T helper cells leads to activation and proliferation of cytotoxic T cells and lymphokine-activated killer cells and the release of IL-4 and IL-6. In addition, IL-2 promotes release of interferon gamma as well as tumor necrosis factor and other proinflammatory cytokines. Therapeutic options to 'downregulate' this cascade have gradually evolved from global nonspecific immunosuppressive techniques (total body irradiation, antilymphocyte serum) to increasingly specific modalities currently being studied, including monoclonal antibodies against the IL-2 receptor (thus targeting only vigorously proliferating T cells), antibodies against specific cytokines (interferon gamma, tumor necrosis factor), and now 'designer' antibody-toxin **conjugate** molecules that deliver toxins to selected receptor targets. Finally, work continues toward inducing preoperative antigen-specific (graft) tolerance, including utilization of gene transfection techniques to transfect donor major histocompatibility complex antigens to recipients before surgery, which has been shown to prolong murine cardiac allografts, perhaps by priming specific suppressor cells. Further understanding of the initiation of, and subsequent events in, transplantation rejection will lead to increasingly effective prolongation of graft survival while minimizing adverse effects on the host.

L12 ANSWER 13 OF 13 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1993082701 EMBASE Prevention and treatment of acute GvHD - New modalities. Herve P.; Tiberghien P.; Racadot E.; Plouvier E.; Cahn J.Y.. P. Herve, BMT Unit, Besancon, France. Bone Marrow Transplantation Vol. 11, No. SUPPL. 1, pp. 103-106 1993. ISSN: 0268-3369. CODEN: BMTRE9. Pub. Country: United Kingdom. Language: English. Entered STN: 930425. Last Updated on STN: 930425

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L14 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

2007:64966 Document No. 147:317664 Photo-cross-linked small-molecule microarrays as chemical genomic tools for dissecting protein-ligand interactions. Kano, Naoki; Asami, Aya; Kawatani, Makoto; Honda, Kaori; Kumashiro, Saori; Takayama, Hiroshi; Simizu, Siro; Amemiya, Tomoyuki; Kondoh, Yasumitsu; Hatakeyama, Satoru; Tsuganezawa, Keiko; Utata, Rei; Tanaka, Akiko; Yokoyama, Shigeyuki; Tashiro, Hideo; Osada, Hiroyuki (Antibiotics Laboratory Discovery Research Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama, 351-0198, Japan). Chemistry--An Asian Journal, 1(6), 789-797 (English) 2006. CODEN: CAAJBI. ISSN: 1861-4728. Publisher: Wiley-VCH Verlag GmbH & Co. KGaA.

AB The authors have developed a unique photo-crosslinking approach for immobilizing a variety of small mols. in a functional-group-independent manner. The authors' approach depends on the reactivity of the carbene species generated from trifluoromethylaryldiazirine upon UV irradiation. It

was demonstrated in model expts. that the photogenerated carbenes were able to react with every small mol. tested, and they produced multiple **conjugates** in most cases. It was also found in on-array immobilization expts. that various small mols. were immobilized, and the immobilized small mols. retained their ability to interact with their binding proteins. With this approach, photo-crosslinked microarrays of about 2000 natural products and drugs were constructed. This photo-crosslinked microarray format was found to be useful not merely for ligand screening but also to study the structure-activity relationship, i.e., the relationship between the structural motif (or pharmacophore) found in small mols. and its binding affinity toward a protein, by taking advantage of the nonselective nature of the photo-crosslinking process.

L14 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

2004:182368 Document No. 140:229401 Three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands. Come, Jon H.; Becker, Frank; Kley, Nikolai A.; Reichel, Christoph (Gpc Biotech Inc., USA; Gpc Biotech AG). U.S. Pat. Appl. Publ. US 2004043388 A1 20040304, 238 pp., Cont.-in-part of U.S. Ser. No. 91,177. (English). CODEN: USXXCO. APPLICATION: US 2002-234985 20020903. PRIORITY: US 2002-91177 20020304; US 2001-329437P 20011015; US 2001-278233P 20010323; US 2001-272932P 20010302.

AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Preparation of compds., e.g a methotrexate moiety linked by a polyethylene glycol moiety to dexamethasone, is described.

L14 ANSWER 3 OF 6 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

2002:294009 Document No.: PREV200200294009. Synthetic bifunctional molecules containing a drug moiety and presenter protein ligand. Briesewitz, Roger [Inventor, Reprint author]; Crabtree, Gerald R. [Inventor]; Wandless, Thomas [Inventor]; Ray, Gregory Thomas [Inventor]; Vogel, Kurt William [Inventor]. Mountain View, CA, USA. ASSIGNEE: The Board of Trustees of the Leland Stanford Jr. University; The Howard Hughes Medical Institute, Chevy Chase, MD, USA. Patent Info.: US 6372712 20020416. Official Gazette of the United States Patent and Trademark Office Patents, (Apr. 16, 2002) Vol. 1257, No. 3. <http://www.uspto.gov/web/menu/patdata.html>. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB Bifunctional molecules and methods for their use in the production of binary complexes in a host are provided. The bifunctional molecule is a **conjugate** of a drug moiety and a presenter protein ligand. The molecular weight of the bifunctional molecule is preferably less than about 5000 daltons, and the drug moiety may have a molecular weight of from about 50 to 2000 daltons. The drug moiety and presenter protein ligand may be covalently linked directly or through a linking group. The drug moiety binds to a drug target such as a protein and the presenter protein ligand binds to a presenter protein that is not the drug target such as extracellular or intracellular protein. Presenter proteins include peptidyl prolyl isomerase (**FKBP**), Heat Shock Protein 90 (**Hsp90**), steroid hormone receptors, cytoskeletal proteins, albumin and vitamin receptors. When the presenter protein is **FKBP**, ligands include **FK506**, **rapamycin** and **cyclosporin A** which may have an introduced functional group such as hydroxyl, amino, carboxyl, aldehyde, carbonate, carbamate, azide, thiol or ester for attaching the drug moiety. In the methods of use, an effective amount of the bifunctional molecule is administered to the host. The bifunctional molecule binds to the presenter protein to produce a binary complex such that the drug exhibits at least one of improved affinity, specificity or selectivity as compared to the corresponding free drug. The methods and bifunctional molecules find use in a variety of therapeutic applications.

L14 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

2001:380753 Document No. 134:361402 Bifunctional inhibitor molecules, their use in the disruption of protein-protein interactions and therapeutic

applications. Crabtree, Gerald R.; Stankunas, Kryn; Briesewitz, Roger; Wandless, Thomas (The Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 2001036612 A1 20010525, 30 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US31695 20001117. PRIORITY: US 1999-PV166675 19991119.

AB Bifunctional inhibitor mols. and methods for their use in the inhibition of protein-protein interactions are provided. The subject bifunctional inhibitor mols. are **conjugates** of a target protein ligand and a blocking protein ligand, where these two moieties are optionally joined by a linking group. In the subject methods, an effective amount of the bifunctional inhibitor mol. is administered to a host in which the inhibition of a protein-protein interaction is desired. The bifunctional inhibitor mol. simultaneously binds to its corresponding target and blocking proteins to produce a tripartite complex that inhibits the target protein-protein interaction. The subject methods and compns. find use in a variety of applications, including therapeutic applications.

L14 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
2001:91445 Document No. 134:158472 Synthetic transcriptional modulator ligands and their use in gene regulation with chimeric proteins containing DNA-binding domains and ligand-binding domains. Verdine, Gregory L.; Nyanguile, Origene (President and Fellows of Harvard College, USA). U.S. US 6183965 B1 20010206, 38 pp., Cont.-in-part of U.S. Ser. No. 987,912. (English). CODEN: USXXAM. APPLICATION: US 1998-208057 19981209. PRIORITY: US 1997-987912 19971209.

AB Novel synthetic transcriptional modulators having at least one selected ligand linked to at least one transcriptional modulating portion are described. The transcriptional modulators of the present invention can include a ligand linked to a chemical moiety. These transcriptional modulators can be used to selectively control gene expression and to identify components of the transcriptional machinery. Thus, the covalent **conjugate** (designated L-1) of **FK506** and a 29-amino acid peptide of herpes simplex virus VP16 activator domain stimulates transcription in the presence of the chimeric GAL4-**FKBP** protein, but was unable to stimulate in the absence of GAL4-**FKBP** and the activation potential was significantly reduced in the presence of added **rapamycin** or GST-**FKBP**. Since acyclic peptides having the natural L stereochem. configuration are highly susceptible to proteolysis, the analogous **conjugate** (D-1) bearing nonnatural D stereochem. is prepared D-1 reproducibly stimulated transcription to a significant extent, though to a slightly lesser extent than L-1. The synthesis of a combinatorial compound library is also provided, and various library components are active transcriptional modulators when coupled to the HATU analog of **FK506**.

L14 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
1999:390464 Document No. 131:39762 Method to identify transcriptional modulators. Verdine, Gregory L.; Nyanguile, Origene (President and Fellows of Harvard College, USA). PCT Int. Appl. WO 9930164 A1 19990617, 90 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US26101 19981209. PRIORITY: US 1997-987912 19971209.

AB Novel synthetic transcriptional modulators having at least one selected ligand linked to at least one transcriptional modulating portion are described. The transcriptional modulators of the present invention can include a ligand linked to a chemical moiety. These transcriptional modulators can be used to selectively control gene expression and to identify components of the transcriptional machinery.

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L15 378759 TARGETING

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L16 30227 L15 AND INTRACELLULAR

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L19 ANSWER 1 OF 7 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1998237002 EMBASE Targeted expansion of genetically modified bone marrow cells. Jin L.; Siritanaratkul N.; Emery D.W.; Richard R.E.; Kaushansky K.; Papayannopoulou T.; Blau C.A.. C.A. Blau, Div. of Hematology and Med. Genetics, Mailstop 357710, Health Sciences Building, Seattle, WA 98195, United States. tblau@u.washington.edu. Proceedings of the National Academy of Sciences of the United States of America Vol. 95, No. 14, pp. 8093-8097 7 Jul 1998.

Refs: 28.

ISSN: 0027-8424. CODEN: PNASA6

Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 19980827. Last Updated on STN: 19980827

AB The ability to specifically target a mitogenic signal to a population of genetically modified primary cells would have potential applications both for gene and cell therapy. Toward this end, a gene encoding a fusion protein containing the FK506-binding protein FKBP12, fused to the intracellular portion of the receptor for thrombopoietin (mpl), was introduced into primary murine bone marrow cells. Dimerization of this fusion protein through the addition of a dimeric form of the drug FK506, called FK1012, resulted in a marked proliferative expansion of marrow cells that was restricted to the genetically modified population. FK1012's proliferative effect was sustained and reversible. An apparent preference for differentiation along the megakaryocytic lineage was observed. This approach allows for the specific delivery of a mitogenic signal to a population of genetically modified primary cells and may have applications for studies in hematopoiesis and receptor biology, and for gene and cell therapy.

L19 ANSWER 2 OF 7 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1997005382 EMBASE The immunosuppressant FK506 and its nonimmunosuppressive analog L- 685,818 are toxic to Cryptococcus neoformans by inhibition of a common target protein. Odom A.; Del Poeta M.; Perfect J.; Heitman J.. J. Heitman, 322 CARL Bldg., Duke University Medical Center, Box 3546, Research Dr., Durham, NC 27710, United States. Antimicrobial Agents and Chemotherapy Vol. 41, No. 1, pp. 156-161 1997.

Refs: 52.

ISSN: 0066-4804. CODEN: AMACCQ

Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 970128. Last Updated on STN: 970128

AB The immunosuppressant FK506 (tacrolimus) is an antifungal natural product macrolide that suppresses the immune system by blocking T-cell activation.

In complex with the **intracellular** protein **FKBP12**, FK506 inhibits calcineurin, a Ca(2+)-calmodulin-dependent serine-threonine protein phosphatase. We recently reported that growth of the opportunistic fungal pathogen *Cryptococcus neoformans* is resistant to FK506 at 24°C but sensitive at 37°C and that calcineurin, the target of **FKBP12**-FK506, is required for growth at 37°C in vitro and pathogenicity in vivo. These findings identify calcineurin as a potential antifungal drug target. In previous studies the calcineurin inhibitor cyclosporin A (CsA) was effective against murine pulmonary infections but exacerbated cryptococcal meningitis in rabbits and mice, likely because CsA does not cross the blood-brain barrier. Although we find that FK506 penetrates the CNS, FK506 also exacerbates cryptococcal meningitis in rabbits. Thus, FK506 immunosuppression outweighs antifungal action in vivo. Like FK506, the nonimmunosuppressive FK506 analog L-685,818 is toxic to *C. neoformans* in vitro at 37°C but not at 24°C, and FK506-resistant mutants are resistant to L-685,818, indicating a similar mechanism of action. Fluconazole-resistant *C. neoformans* clinical isolates were also found to be susceptible to both FK506 and L-685,818. Our findings identify calcineurin as a novel antifungal drug target and suggest the nonimmunosuppressive FK506 analog L-685,818 or other congeners warrant further consideration as antifungal drugs for *C. neoformans*.

L19 ANSWER 3 OF 7 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1994215832 EMBASE A mammalian protein targeted by G1-arresting rapamycin-receptor complex. Brown E.J.; Albers M.W.; Tae Bum Shin; Ichikawa K.; Keith C.T.; Lane W.S.; Schreiber S.L.. S.L. Schreiber, Department of Chemistry, Howard Hughes Medical Institute, 12 Oxford Street, Cambridge, MA 02138, United States. Nature Vol. 369, No. 6483, pp. 756-758 1994.

ISSN: 0028-0836. CODEN: NATUAS

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 940817. Last Updated on STN: 940817

AB The structurally related natural products rapamycin and FK506 bind to the same **intracellular** receptor, **FKBP12**, yet the resulting complexes interfere with distinct signalling pathways. **FKBP12**-rapamycin inhibits progression through the G1 phase of the cell cycle in osteosarcoma, liver and T cells as well as in yeast, and interferes with mitogenic signalling pathways that are involved in G1 progression, namely with activation of the protein p70(S6k) (refs 5, 11-13) and cyclin-dependent kinases. Here we isolate a mammalian FKBP-rapamycin-associated protein (FRAP) whose binding to structural variants of rapamycin complexed to **FKBP12** correlates with the ability of these ligands to inhibit cell-cycle progression. Peptide sequences from purified bovine FRAP were used to isolate a human cDNA clone that is highly related to the DRR1/TOR1 and DRR2/TOR2 gene products from *Saccharomyces cerevisiae*. Although it has not been previously demonstrated that either of the DRR/TOR gene products can bind the FKBP-rapamycin complex directly, these yeast genes have been genetically linked to a rapamycin-sensitive pathway and are thought to encode lipid kinases.

L19 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

2001:279524 Document No. 134:290424 Method for targeted degradation of **intracellular** proteins in vivo or ex vivo. Coffino, Philip; Li, Xianqiang (The Regents of the University of California, USA). U.S. US 6217864 B1 20010417, 29 pp., Cont.-in-part of U.S. 5,866,121. (English). CODEN: USXXAM. APPLICATION: US 1999-243273 19990202. PRIORITY: US 1996-603575 19960223.

AB A method for in vivo selective targeted degradation of **intracellular** proteins in situ by inducing in vivo or ex vivo in cells a production of dual-function protein comprising N-terminal domain as well as a C-terminal domain or delivering the dual-function protein. The N-terminal domain of

the dual-function protein destabilizes the target protein and directs its degradation when linked to it through a linker between the target protein and between the protein agent of the invention. The protein degradation directing N-terminal domain is a subregion within the first 97 amino acids corresponding to the N-terminus of protein antizyme.

L19 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

1998:734993 Document No. 130:1173 Regulated apoptosis by chimeric proteins binding to FK506-type and cyclosporin-type ligands. Crabtree, Gerald R.; Schreiber, Stuart L.; Spencer, David M.; Wandless, Thomas J.; Belshaw, Peter (President & Fellows of Harvard College, USA; Board of Trustees of Leland Stanford Jr. University). U.S. US 5834266 A 19981110, 104 pp., Cont.-in-part of U.S. Ser. No. 179,143, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1994-292597 19940818. PRIORITY: US 1993-17931 19930212; US 1993-92977 19930716; US 1993-93499 19930716; US 1994-179143 19940107; US 1994-179748 19940107.

AB A general procedure is described for the regulated (inducible) dimerization or oligomerization of **intracellular** proteins and methods and materials are presented for using that procedure to regulatably initiate cell-specific apoptosis (programmed cell death) in genetically engineered cells. The procedure involves chimeric (or fused) proteins, DNA constructs encoding them, and ligand mols. capable of oligomerizing the chimeric proteins. The chimeric proteins contain at least one ligand-binding (or receptor) domain fused to an action domain capable of initiating apoptosis within a cell (e.g., Fas or tumor necrosis factor receptor), and may also contain addnl. domains for (1) the regulatable or constitutive expression of desired genes and (2) **intracellular targeting**. The chimeric proteins are capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline, or a steroid ligand. One such chimeric protein is myristoylated CD3/**FKBP12** (MZFP3E) receptor consisting of (1) a c-src fragment sufficient for myristoylation, (2) the cytoplasmic tail of ζ (a component of the B cell receptor), (3) 3 consecutive domains of the **FKBP12** immunophilin, and (4) a flu epitope tag; oligomerization/apoptosis is induced by a dimeric derivative of FK506. Syntheses are reported for the preparation of dimeric and "bumped" (containing steric bulky groups) derivs. of FK506 and cyclosporin A. The overall procedures allows ligand-mediated oligomerization for regulated gene therapy.

L19 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

1996:350220 Document No. 125:27701 Regulatable elimination of gene expression, gene product function and engineered host cells, and its application in gene therapy. Brugge, Joan S.; Crabtree, Gerald R. (Ariad Gene Therapeutics, Inc., USA). PCT Int. Appl. WO 9606111 A1 19960229, 141 pp. DESIGNATED STATES: W: AU, CA, GB, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US10591 19950818. PRIORITY: US 1994-292595 19940818; US 1994-292596 19940818; US 1994-292597 19940818.

AB Materials and methods are disclosed for regulated obstruction of the expression of a target gene or the biol. effect of its gene product in genetically engineered cells or organisms containing them. Aspects of the invention are exemplified by recombinant modifications of host cells and their use in vitro and in vivo for the regulatable blockade of expression of a target gene, for interference with the function or effect of a target gene product or for the regulatable elimination of a target gene. Synthesis of oligomer of ligands such as FK506 and cyclosporin A, and regulation of programmed cell death with immunophilin-Fas antigen chimeras were demonstrated.

L19 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

1995:541403 Document No. 122:283855 Regulated apoptosis by chimeric proteins binding to FK506-type and cyclosporin-type ligands. Crabtree, Gerald R.; Schreiber, Stuart L.; Spencer, David M.; Wandless, Thomas J.; Belshaw,

Peter (Board of Trustees of the Leland Stanford Junior University, USA; President and Fellows of Harvard College). PCT Int. Appl. WO 9502684 A1 19950126, 134 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US8008 19940718. PRIORITY: US 1993-93499 19930716; US 1994-179143 19940107; WO 1994-US1617 19940214.

AB A general procedure is described for the regulated (inducible) dimerization or oligomerization of **intracellular** proteins and methods and materials are presented for using that procedure to regulatably initiate cell-specific apoptosis (programmed cell death) in genetically engineered cells. The procedure involves chimeric (or fused) proteins, DNA constructs encoding them, and ligand mols. capable of oligomerizing the chimeric proteins. The chimeric proteins contain at least one ligand-binding (or receptor) domain fused to an action domain capable of initiating apoptosis within a cell, and may also contain addnl. domains for (1) the regulatable or constitutive expression of desired genes and (2) **intracellular targeting**. The chimeric proteins are capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline, or a steroid ligand. One such chimeric protein is myristoylated CD3/**FKBP12** (MZP3E) receptor consisting of (1) a c-src fragment sufficient for myristoylation, (2) the cytoplasmic tail of ζ (a component of the B cell receptor), (3) 3 consecutive domains of the **FKBP12** immunophilin, and (4) a flu epitope tag; oligomerization/apoptosis is induced by a dimeric derivative of FK506. Syntheses are reported for the preparation of dimeric and "bumped" (containing steric bulky groups) derivs. of FK506 and cyclosporin A. The overall procedures allows ligand-mediated oligomerization for regulated gene therapy.

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L22 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN
2002:165031 Document No. 136:195367 NF-AT (nuclear factor, activated T-cell) cytosolic and nuclear polypeptides and their use in screening for immunosuppressive agents. Crabtree, Gerald R.; Northrop, Jeffrey P.; Ho, Steffan N.; Flanagan, William M. (The Board of Trustees of the Leland Stanford Junior University, USA). U.S. US 6352830 B1 20020305, 83 pp., Cont.-in-part of U. S. 5,989,810. (English). CODEN: USXXAM. APPLICATION: US 1999-232346 19990115. PRIORITY: US 1991-749385 19910822; US 1993-124981 19930920; US 1994-228944 19940418; US 1994-260174 19940613; US 1995-507032 19950731.

AB The invention provides novel polypeptides which are associated with the transcription complex NF-AT, and polynucleotides encoding such polypeptides. Specifically, NF-ATc (cytoplasmic) and NF-ATn (nuclear) proteins associate in a complex that interacts with an NF-AT DNA binding sequence which may be studied using gel mobility shift assays. The NF-ATc is translocated to the nucleus by an immunosuppressive agent. Immunosuppressive agents may be identified by contacting a NF-ATc protein with a test agent and determining the level of said complex formation.

Furthermore, the NF-ATc or NF-ATn proteins may be immobilized. An NF-AT regulated enhancer region may be linked to a nucleic acid that encodes a protein essential for cell proliferation or viability to assay for nuclear translocation of NF-ATc. Also provided are antibodies to NF-AT polypeptides, polynucleotide hybridization probes and PCR amplification probes for detecting polynucleotides which encode such polypeptides. Transgenes which encode such polypeptides, homologous **targeting** constructs that encode such polypeptides and/or homologously integrate in or near endogenous genes encoding such polypeptides are provided. Non-human transgenic animals which comprise functionally disrupted endogenous genes that normally encode such polypeptides, and transgenic nonhuman animals which comprise transgenes encoding such polypeptides are also provided. Methods for detecting T cells (including activated T cells) in a cellular sample and methods for treating hyperactive or hypoactive T cell conditions are also provided. Methods for screening for immunomodulatory agents, methods for diagnostic staging of lymphocyte differentiation, methods for producing NF-AT proteins for use as research or diagnostic reagents, methods for producing antibodies reactive with the novel polypeptides, and methods for producing transgenic nonhuman animals are other embodiments of the invention. Methods and agents for activation of NF-AT dependent transcription, including agents which interfere with the production, modification of nuclear or cytoplasmic subunits, or the nuclear import of the cytoplasmic subunits are provided. In particular, screening tests for novel immunosuppressants are provided based upon the ability of NF-AT to activate transcription.

L22 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

1998:734993 Document No. 130:1173 Regulated apoptosis by chimeric proteins binding to FK506-type and cyclosporin-type ligands. Crabtree, Gerald R.; Schreiber, Stuart L.; Spencer, David M.; Wandless, Thomas J.; Belshaw, Peter (President & Fellows of Harvard College, USA; Board of Trustees of Leland Stanford Jr. University). U.S. US 5834266 A **19981110**, 104 pp., Cont.-in-part of U.S. Ser. No. 179,143, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1994-292597 19940818. PRIORITY: US 1993-17931 19930212; US 1993-92977 19930716; US 1993-93499 19930716; US 1994-179143 19940107; US 1994-179748 19940107.

AB A general procedure is described for the regulated (inducible) dimerization or oligomerization of **intracellular** proteins and methods and materials are presented for using that procedure to regulatably initiate cell-specific apoptosis (programmed cell death) in genetically engineered cells. The procedure involves chimeric (or fused) proteins, DNA constructs encoding them, and ligand mols. capable of oligomerizing the chimeric proteins. The chimeric proteins contain at least one ligand-binding (or receptor) domain fused to an action domain capable of initiating apoptosis within a cell (e.g., Fas or tumor necrosis factor receptor), and may also contain addnl. domains for (1) the regulatable or constitutive expression of desired genes and (2) **intracellular targeting**. The chimeric proteins are capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline, or a steroid ligand. One such chimeric protein is myristoylated CD3/FKBP12 (MZFP3E) receptor consisting of (1) a c-src fragment sufficient for myristoylation, (2) the cytoplasmic tail of ζ (a component of the B cell receptor), (3) 3 consecutive domains of the FKBP12 **immunophilin**, and (4) a flu epitope tag; oligomerization/apoptosis is induced by a dimeric derivative of FK506. Syntheses are reported for the preparation of dimeric and "bumped" (containing steric bulky groups) derivs. of FK506 and cyclosporin A. The overall procedures allows ligand-mediated oligomerization for regulated gene therapy.

L22 ANSWER 3 OF 10 MEDLINE on STN

1998169374. PubMed ID: 9501079. A novel multi-functional chloroplast protein: identification of a 40 kDa **immunophilin**-like protein located in the thylakoid lumen. Fulgosi H; Vener A V; Altschmied L; Herrmann R G; Andersson B. (Botanisches Institut der Ludwig-Maximilians-

Universitat, Menzinger Strasse 67, D-8000 Munchen, Germany.) The EMBO journal, (1998 Mar 16) Vol. 17, No. 6, pp. 1577-87. Journal code: 8208664. ISSN: 0261-4189. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We describe the identification of the first **immunophilin** associated with the photosynthetic membrane of chloroplasts. This complex 40 kDa **immunophilin**, designated TLP40 (thylakoid lumen PPIase), located in the lumen of the thylakoids, was found to play a dual role in photosynthesis involving both biogenesis and intraorganelle signalling. It originates in a single-copy nuclear gene, is made as a precursor of 49.2 kDa with a bipartite luminal **targeting** transit peptide, and is characterized by a structure including a cyclophilin-like C-terminal segment of 20 kDa, a predicted N-terminal leucine zipper and a potential phosphatase-binding domain. It can exist in different oligomeric conformations and attach to the inner membrane surface. It is confined predominantly to the non-appressed thylakoid regions, the site of protein integration into the photosynthetic membrane. The isolated protein possesses peptidyl-prolyl cis-trans isomerase protein folding activity characteristic of **immunophilins**, but is not inhibited by cyclosporin A. TLP40 also exerts an effect on dephosphorylation of several key proteins of photosystem II, probably as a constituent of a transmembrane signal transduction chain. This first evidence for a direct role of **immunophilins** in a photoautotrophic process suggests that light-mediated protein phosphorylation in photosynthetic membranes and the role of the thylakoid lumen are substantially more complex than anticipated.

L22 ANSWER 4 OF 10 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1998243690 EMBASE Molecular chaperones and subcellular trafficking of steroid receptors. DeFranco D.B.; Ramakrishnan C.; Tang Y.. D.B. DeFranco, Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA 15260, United States. dod1@vms.cis.pitt.edu. Journal of Steroid Biochemistry and Molecular Biology Vol. 65, No. 1-6, pp. 51-58 Apr 1998.

Refs: 66.

ISSN: 0960-0760. CODEN: JSBBEZ

S 0960-0760(97)00177-5. Pub. Country: United Kingdom. Language: English.

Summary Language: English.

Entered STN: 19980917. Last Updated on STN: 19980917

AB Unliganded steroid receptors exist as heteromeric complexes comprised of heat shock and **immunophilin** proteins that associate either directly or indirectly with receptor carboxyl-terminal ligand-binding domains. Molecular chaperons, and other proteins associated with steroid receptors, play an important role in the maturation of receptors to a hormone-binding competent state. Steroid receptor-associated 90 and 70 kDa heat shock proteins, hsp90 and hsp70, respectively, have well established roles in protein folding in addition to participating in numerous subcellular trafficking pathways. In this review, we discuss the possible roles that molecular chaperons, such as hsp90, hsp70 and DnaJ proteins, have in steroid receptor trafficking within two distinct subcellular compartments, i.e. the cytoplasm and nucleus.

L22 ANSWER 5 OF 10 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1997204492 EMBASE Geldanamycin, a heat shock protein 90-binding benzoquinone ansamycin, inhibits steroid-dependent translocation of the glucocorticoid receptor from the cytoplasm to the nucleus. Czar M.J.; Galigniana M.D.; Silverstein A.M.; Pratt W.B.. W.B. Pratt, Department of Pharmacology, 1301 Med. Sci. Research Building III, Univ. of Michigan Medical School, Ann Arbor, MI 48109-0632, United States. Biochemistry Vol. 36, No. 25, pp. 7776-7785 24 Jun 1997.

Refs: 48.

ISSN: 0006-2960. CODEN: BICHAW

Pub. Country: United States. Language: English. Summary Language: English.

Entered STN: 970731. Last Updated on STN: 970731

AB When they are translated, steroid receptors are assembled into a multiprotein complex containing hsp90, p23, an **immunophilin**, and often some hsp70. Some of the receptors, such as that for progesterone, have nuclear localization signals that are functional in the absence of hormone, and they move into the nucleus when they exist in the same multiprotein heterocomplex with hsp90. Other receptors, such as the glucocorticoid receptors, are localized predominantly in the cytoplasm in the absence of hormone and move into the nucleus in a hormone-dependent fashion. We have previously proposed that hsp90 and the **immunophilin** play a role in receptor trafficking [Pratt, W.B. (1993) J. Biol. Chemical 268, 21455-21458]. In this work, we show that treatment of L cells with geldanamycin, a benzoquinone ansamycin that binds to hsp90 and disrupts its function, impedes dexamethasone-dependent trafficking of the glucocorticoid receptor from the cytoplasm to the nucleus. Because geldanamycin treatment of hormone-free cells causes a rapid loss of steroid binding activity, receptors were prebound with dexamethasone by incubating cells with hormone at 0 °C prior to shifting the temperature to 37 °C for 20 min to permit receptor transformation and translocation in the presence or absence of geldanamycin. Geldanamycin does not cause steroid to dissociate from prebound receptors, and it does not inhibit hormone-mediated receptor transformation assayed by conversion to the DNA-binding state. However, as reported previously for the progesterone receptor, geldanamycin blocks assembly of the glucocorticoid receptor hsp90 heterocomplex at an intermediate state of assembly where the receptor is bound to hsp70 and p60, both of which are required components in the assembly mechanism. Our observations support the proposal that dynamic association of receptors with hsp90 is required for receptor translocation from the cytoplasm to the nucleus.

L22 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

1996:350220 Document No. 125:27701 Regulatable elimination of gene expression, gene product function and engineered host cells, and its application in gene therapy. Brugge, Joan S.; Crabtree, Gerald R. (Ariad Gene Therapeutics, Inc., USA). PCT Int. Appl. WO 9606111 A1 19960229, 141 pp. DESIGNATED STATES: W: AU, CA, GB, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US10591 19950818. PRIORITY: US 1994-292595 19940818; US 1994-292596 19940818; US 1994-292597 19940818.

AB Materials and methods are disclosed for regulated obstruction of the expression of a target gene or the biol. effect of its gene product in genetically engineered cells or organisms containing them. Aspects of the invention are exemplified by recombinant modifications of host cells and their use in vitro and in vivo for the regulatable blockade of expression of a target gene, for interference with the function or effect of a target gene product or for the regulatable elimination of a target gene. Synthesis of oligomer of ligands such as FK506 and cyclosporin A, and regulation of programmed cell death with **immunophilin**-Fas antigen chimeras were demonstrated.

L22 ANSWER 7 OF 10 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1996184606 EMBASE A model of protein **targeting** mediated by **immunophilins** and other proteins that bind to hsp90 via tetratricopeptide repeat domains. Owens-Grillo J.K.; Czar M.J.; Hutchison K.A.; Hoffmann K.; Perdew G.H.; Pratt W.B.. W.B. Pratt, Dept. of Pharmacology, 1301 Med. Science Research Bldg. III, Michigan University Medical School, Ann Arbor, MI 48109-0632, United States. Journal of Biological Chemistry Vol. 271, No. 23, pp. 13468-13475 1996. Refs: 72. ISSN: 0021-9258. CODEN: JBCHA3 Pub. Country: United States. Language: English. Summary Language: English. Entered STN: 960716. Last Updated on STN: 960716

AB We have shown recently that the **immunophilins** CyP-40 and FKBP52/hsp56 bind to a common site on hsp90 and that they exist in separate heterocomplexes with the glucocorticoid receptor (GR). FKBP52/hsp56 binds to hsp90 via its tetratricopeptide repeat (TPR) domains, it is not required for GR.ovrhdot.hsp90 heterocomplex assembly, and it is thought to play a role in targeted movement of the GR. In this work we examine the hsp90 binding of four proteins (FKBP52/hsp56, CyP-40, p50, Mas70p) thought to be involved in targeted protein trafficking. FKBP52/hsp56 and CyP-40 (each with three TPRs), localize to the nucleus and nucleoli, respectively, and form relatively weak complexes with hsp90 that are competed by a CyP-40 fragment containing its three TPRs. The p50 component of the Src.ovrhdot.hsp90 and Raf.ovrhdot.hsp90 heterocomplexes localizes to cytoskeletal fibers extending from the perinuclear region to the plasma membrane and forming a rim under the plasma membrane of endothelial cells. p50, Mas70p (seven TPRs), which is a receptor for mitochondrial import, and the p60 (six to eight TPRs) component of the steroid receptor.ovrhdot.hsp90 heterocomplex assembly system bind very tightly to hsp90 in a manner that is not competed by the CyP-40 fragment. However, bacterially expressed p60 blocks the binding of p50, Mas70p, FKBP52/hsp56, and CyP-40 to purified hsp90. The data are consistent with binding of all of these proteins to a site on hsp90 that is a general TPR domain acceptor. Our localization and binding data are used to develop a model in which proteins that are chaperoned by hsp90 move as dynamic complexes to their cellular sites of action, with the TPR-containing protein participating in **targeting** the movement of the complexes.

L22 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

1995:541403 Document No. 122:283855 Regulated apoptosis by chimeric proteins binding to FK506-type and cyclosporin-type ligands. Crabtree, Gerald R.; Schreiber, Stuart L.; Spencer, David M.; Wandless, Thomas J.; Belshaw, Peter (Board of Trustees of the Leland Stanford Junior University, USA; President and Fellows of Harvard College). PCT Int. Appl. WO 9502684 A1 19950126, 134 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US8008 19940718. PRIORITY: US 1993-93499 19930716; US 1994-179143 19940107; WO 1994-US1617 19940214.

AB A general procedure is described for the regulated (inducible) dimerization or oligomerization of **intracellular** proteins and methods and materials are presented for using that procedure to regulatably initiate cell-specific apoptosis (programmed cell death) in genetically engineered cells. The procedure involves chimeric (or fused) proteins, DNA constructs encoding them, and ligand mols. capable of oligomerizing the chimeric proteins. The chimeric proteins contain at least one ligand-binding (or receptor) domain fused to an action domain capable of initiating apoptosis within a cell, and may also contain addnl. domains for (1) the regulatable or constitutive expression of desired genes and (2) **intracellular targeting**. The chimeric proteins are capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline, or a steroid ligand. One such chimeric protein is myristoylated CD3/FKBP12 (MZF3E) receptor consisting of (1) a c-src fragment sufficient for myristoylation, (2) the cytoplasmic tail of ζ (a component of the B cell receptor), (3) 3 consecutive domains of the FKBP12 **immunophilin**, and (4) a flu epitope tag; oligomerization/apoptosis is induced by a dimeric derivative of FK506. Syntheses are reported for the preparation of dimeric and "bumped" (containing steric bulky groups) derivs. of FK506 and cyclosporin A. The overall procedures allows ligand-mediated oligomerization for regulated gene therapy.

L22 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2008 ACS on STN

1995:377088 Document No. 122:153359 Regulated transcription of target genes

with dimeric ligands which cause chimeric receptor proteins to oligomerize and induce gene transcription. Crabtree, Gerald R.; Schreiber, Stuart L.; Spencer, David M.; Wandless, Thomas J.; Belshaw, Peter (Leland Stanford Junior University, USA; Harvard College). PCT Int. Appl. WO 9418317 A1 19940818, 133 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, SK; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US1617 19940214. PRIORITY: US 1993-17931 19930212; US 1993-92977 19930716; US 1994-179748 19940107.

AB A general procedure for regulating (inducing) dimerization or oligomerization of chimeric proteins is presented. The chimeric proteins contain a receptor domain and another protein domain capable of initiating a biol. process. The chimeric proteins can be induced to associate by treating the cells or organisms that harbor them with cell-permeable, synthetic ligands. The dimers/oligomers bind to a transcription control element and stimulate transcription of the gene to which it is associated. The syntheses of FK-506 dimers are presented. Such dimers were used to induce: (1) the **intracellular** aggregation of the cytoplasmic tail of the zeta chain of the T cell receptor (TCR)-CD3 complex thereby leading to signaling and transcription of a reporter gene, (2) the homodimerization of the cytoplasmic tail of the Fas receptor thereby leading to cell-specific apoptosis (programmed cell death) and (3) the heterodimerization of a DNA-binding domain (Gal4) and a transcription-activation domain (VP16) thereby leading to direct transcription of a reporter gene.

L22 ANSWER 10 OF 10 MEDLINE on STN DUPLICATE 1
94339699. PubMed ID: 8061522. pCyP B: a chloroplast-localized, heat shock-responsive cyclophilin from fava bean. Luan S; Lane W S; Schreiber S L. (Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138.) The Plant cell, (1994 Jun) Vol. 6, No. 6, pp. 885-92. Journal code: 9208688. ISSN: 1040-4651. Pub. country: United States. Language: English.

AB When the immunosuppressants cyclosporin A (CsA) and FK506 bind to their **intracellular** receptors (immunophilins), they form complexes that bind to calcineurin and block calcineurin-dependent signaling pathways in immune cells. Previously, we reported that higher plants also express **immunophilins** and have a Ca(2+)-dependent signaling pathway sensitive to **immunophilin**-ligand complexes. Based on an N-terminal peptide sequence of a chloroplast-localized cyclophilin (pCyP B), we isolated a cDNA clone encoding the preprotein of the cyclophilin. The deduced amino acid sequence of this cDNA starts with a putative transit sequence for chloroplast **targeting**. The mature pCyP B protein has rotamase activity with low-substrate specificity. Enzyme activity was inhibited by CsA with an inhibition constant of 3.9 nM. Similar to other CyPs from mammalian cells, pCyP B, when complexed with CsA, inhibited the phosphatase activity of bovine calcineurin. The mRNA level of pCyP B was high in leaf tissue but was not detectable in roots. Expression of the transcript in the leaf tissues was regulated by light and induced by heat shock. These findings illustrate the conserved nature of cyclophilin proteins among all of the eukaryotes and suggest that cyclophilins have a unique mode of regulation in higher plants.

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L23 2786 (BRISEWITZ R?/AU OR CRABTREE G?/AU OR WANDLESS T?/AU)

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L24 4 L23 AND INTRACELLULAR TARGETING

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L25 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

1998:734993 Document No. 130:1173 Regulated apoptosis by chimeric proteins binding to FK506-type and cyclosporin-type ligands. **Crabtree, Gerald R.**; Schreiber, Stuart L.; Spencer, David M.; **Wandless, Thomas J.**; Belshaw, Peter (President & Fellows of Harvard College, USA; Board of Trustees of Leland Stanford Jr. University). U.S. US 5834266 A 19981110, 104 pp., Cont.-in-part of U.S. Ser. No. 179,143, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1994-292597 19940818. PRIORITY: US 1993-17931 19930212; US 1993-92977 19930716; US 1993-93499 19930716; US 1994-179143 19940107; US 1994-179748 19940107.

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L25 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

1996:350220 Document No. 125:27701 Regulatable elimination of gene expression, gene product function and engineered host cells, and its application in gene therapy. Brugge, Joan S.; **Crabtree, Gerald R.** (Ariad Gene Therapeutics, Inc., USA). PCT Int. Appl. WO 9606111 A1 19960229, 141 pp. DESIGNATED STATES: W: AU, CA, GB, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US10591 19950818. PRIORITY: US 1994-292595 19940818; US 1994-292596 19940818; US 1994-292597 19940818.

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L25 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

1995:541403 Document No. 122:283855 Regulated apoptosis by chimeric proteins binding to FK506-type and cyclosporin-type ligands. **Crabtree, Gerald R.**; Schreiber, Stuart L.; Spencer, David M.; **Wandless, Thomas J.**; Belshaw, Peter (Board of Trustees of the Leland Stanford Junior University, USA; President and Fellows of Harvard College). PCT Int. Appl. WO 9502684 A1 19950126, 134 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN;

RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US8008 19940718. PRIORITY: US 1993-93499 19930716; US 1994-179143 19940107; WO 1994-US1617 19940214.

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L25 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN

1995:377088 Document No. 122:153359 Regulated transcription of target genes with dimeric ligands which cause chimeric receptor proteins to oligomerize and induce gene transcription. **Crabtree, Gerald R.**; Schreiber, Stuart L.; Spencer, David M.; **Wandless, Thomas J.**; Belshaw, Peter (Leland Stanford Junior University, USA; Harvard College). PCT Int. Appl. WO 9418317 A1 19940818, 133 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, SK; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US1617 19940214. PRIORITY: US 1993-17931 19930212; US 1993-92977 19930716; US 1994-179748 19940107.

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COST IN U.S. DOLLARS

SINCE FILE
ENTRY

TOTAL
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FULL ESTIMATED COST

200.28

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE
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CA SUBSCRIBER PRICE

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